

**Neutrophil counts and the risk of new-onset proteinuria in hypertensive patients**

**Supplemental Material**

**Figure S1.** Flow chart of the participants

**Table S1.** Characteristics of the included and excluded participants

**Table S2.** Characteristics of study participants by quintiles of neutrophil counts in the enalapril only group

**Table S3.** The relationship of white blood cell (WBC) counts with new-onset proteinuria in the enalapril only group

**Table S4.** The relationship of neutrophil counts with new-onset proteinuria in the enalapril only group with further adjustment for lymphocyte counts

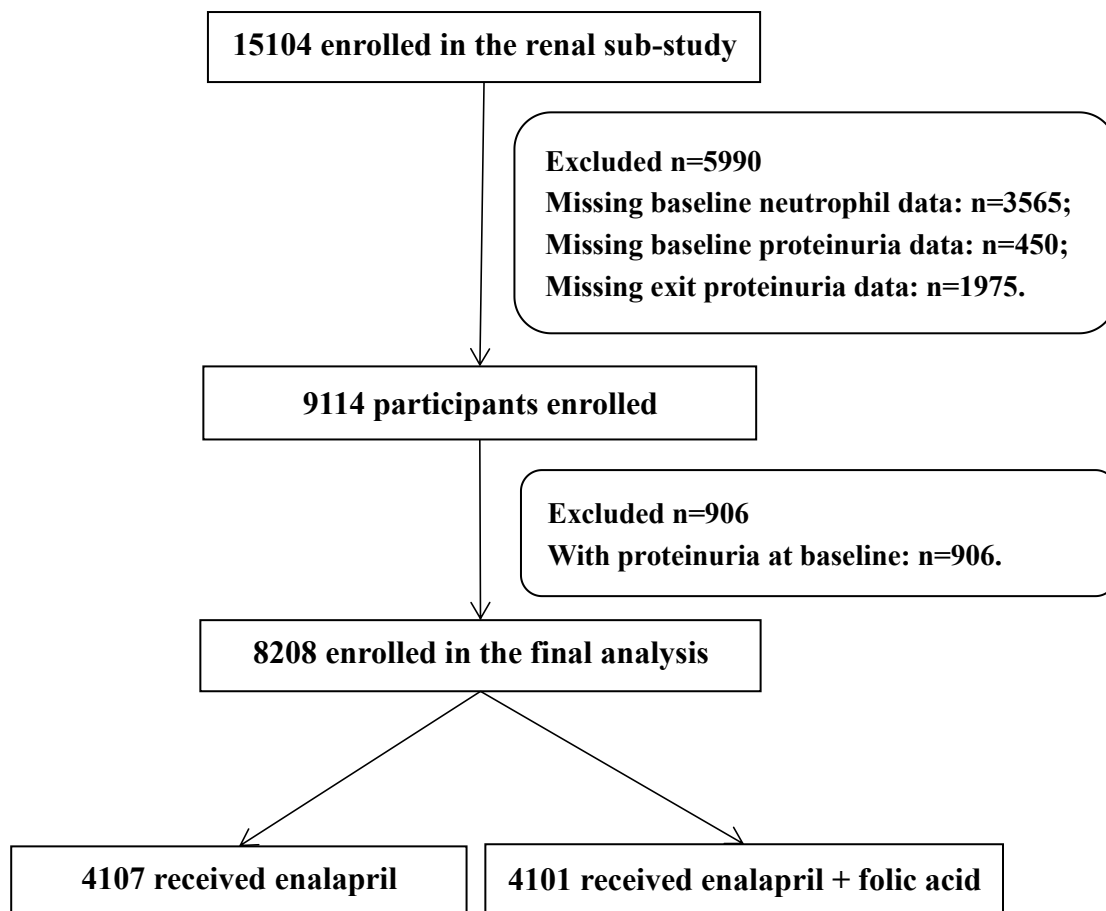
**Table S5.** Concomitant medication usage during the treatment period by quintiles of neutrophil counts in the enalapril only group

**Table S6.** The relationship of neutrophil counts with new-onset proteinuria in the enalapril only group with further adjustment for calcium channel blocker usage during the treatment period

**Table S7.** Effect modification of neutrophil counts on efficacy of folic acid in prevention of new-onset proteinuria with further adjustment for lymphocyte counts

**Table S8.** Effect modification of neutrophil counts on efficacy of folic acid in prevention of new-onset proteinuria with further adjustment for calcium channel blocker usage during the treatment period

**Table S9.** Effect modification of neutrophil counts on efficacy of folic acid in prevention of new-onset proteinuria with further adjustment for annual rate of eGFR decline during the treatment period



**Figure S1. Flow chart of the participants**

**Table S1. Characteristics of the included and excluded participants**

Variables	Excluded	Included
N	5990	9114
Age, year	59.4 ± 7.8	59.5 ± 7.4
Male, No. (%)	2441 (40.8)	3461 (38.0)
Body mass index, kg/m <sup>2</sup>	25.6 ± 3.6	25.7 ± 3.6
Current smoking, No. (%)	1512 (25.3)	1905 (20.9)
<b>Blood pressure, mmHg</b>		
Baseline SBP	168.9 ± 20.9	167.9 ± 21.0
Baseline DBP	95.9 ± 12.1	95.0 ± 11.8
Time-averaged SBP	140.4 ± 11.7	139.6 ± 11.0
Time-averaged DBP	84.1 ± 7.7	83.6 ± 7.3
<b>Laboratory results</b>		
Total cholesterol, mmol/L	5.9 ± 1.2	5.6 ± 1.2
Triglycerides, mmol/L	1.7 ± 0.9	1.7 ± 1.4
HDL-C, mmol/L	1.4 ± 0.4	1.3 ± 0.4
Fasting glucose, mmol/L	6.1 ± 1.9	6.0 ± 1.7
Uric acid, µmol/L	294.5 ± 79.0	294.0 ± 79.4
eGFR, mL/min/1.73m <sup>2</sup>	93.6 ± 12.8	94.5 ± 12.8
Folate, ng/mL	7.5 ± 3.1	7.8 ± 3.3
Total homocysteine, µmol/L	14.9 ± 9.5	14.5 ± 8.7
White blood cell counts, 10 <sup>9</sup> /L	6.6 ± 2.0	6.6 ± 1.9
Neutrophil counts, 10 <sup>9</sup> /L	4.0 ± 1.5	3.9 ± 1.6
Lymphocyte counts, 10 <sup>9</sup> /L	2.1 ± 0.7	2.1 ± 0.7
<b>Medication use, No. (%)</b>		
Antihypertensive drugs	2854 (47.6)	4601 (50.5)
Glucose-lowering drugs	114 (1.9)	161 (1.8)
Lipid-lowering drugs	52 (0.9)	76 (0.8)
Antiplatelet drugs	268 (4.5)	317 (3.5)

\*Variables are presented as Mean ± SD or n (%)

**Abbreviations:** SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

**Table S2. Characteristics of study participants by quintiles of neutrophil counts in the enalapril only group.**

Variables	Neutrophil counts, 10 <sup>9</sup> /L					P value
	Q1(<2.7)	Q2(2.7-<3.3)	Q3(3.3-<4.0)	Q4(4.0-<4.8)	Q5(≥4.8)	
N	700	799	911	804	893	
Age, year	58.3 ± 7.1	59.1 ± 7.5	59.4 ± 7.4	60.2 ± 7.4	60.0 ± 7.7	<0.001
Male, No. (%)	212 (30.3)	280 (35.0)	361 (39.6)	355 (44.2)	346 (38.7)	<0.001
Body mass index, kg/m <sup>2</sup>	25.3 ± 3.5	25.7 ± 3.4	25.9 ± 3.5	25.7 ± 3.6	25.4 ± 3.7	0.016
Current smoking, No. (%)	108 (15.4)	139 (17.4)	195 (21.4)	205 (25.5)	228 (25.5)	<0.001
<b>Blood pressure, mmHg</b>						
Baseline SBP	165.4 ± 19.8	167.0 ± 20.0	167.8 ± 20.8	168.0 ± 20.3	168.4 ± 21.0	0.038
Baseline DBP	94.1 ± 11.0	94.2 ± 11.5	95.1 ± 12.1	94.9 ± 11.5	94.9 ± 12.2	0.264
Time-averaged SBP	137.9 ± 10.5	139.3 ± 10.9	139.5 ± 10.6	139.4 ± 11.2	140.2 ± 10.8	0.001
Time-averaged DBP	83.6 ± 6.8	83.4 ± 7.5	83.7 ± 7.2	83.4 ± 7.3	83.3 ± 7.4	0.718
<b>Laboratory results</b>						
Total cholesterol, mmol/L	5.5 ± 1.1	5.6 ± 1.2	5.6 ± 1.1	5.6 ± 1.1	5.7 ± 1.3	0.005
Triglycerides, mmol/L	1.5 ± 0.7	1.7 ± 0.9	1.7 ± 1.1	1.7 ± 0.9	1.8 ± 1.0	<0.001
HDL-C, mmol/L	1.4 ± 0.4	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.4	0.085
Fasting glucose, mmol/L	5.9 ± 1.3	6.1 ± 1.7	5.9 ± 1.6	6.0 ± 1.6	6.1 ± 1.8	0.045
Uric acid, μmol/L	276.6 ± 74.9	288.5 ± 74.4	299.1 ± 80.1	299.2 ± 84.0	293 ± 76.4	<0.001
eGFR, mL/min/1.73m <sup>2</sup>	96.5 ± 10.6	95.6 ± 11.7	95.0 ± 12.1	94.0 ± 12.0	94.6 ± 12.3	<0.001
Folate, ng/mL	8.2 ± 3.4	7.8 ± 3.0	7.9 ± 3.0	7.8 ± 3.8	7.6 ± 3.5	0.009
Total homocysteine, μmol/L	13.6 ± 8.6	14.3 ± 8.3	13.9 ± 7.7	14.5 ± 7.8	15.2 ± 9.6	0.002
WBC counts, 10 <sup>9</sup> /L	4.5 ± 0.8	5.5 ± 0.7	6.3 ± 0.7	7.1 ± 0.9	8.9 ± 1.8	<0.001
Neutrophil counts, 10 <sup>9</sup> /L	2.2 ± 0.3	3 ± 0.2	3.6 ± 0.2	4.3 ± 0.2	6.0 ± 2.4	<0.001
Lymphocyte counts, 10 <sup>9</sup> /L	1.8 ± 0.6	2.0 ± 0.6	2.1 ± 0.6	2.2 ± 0.7	2.3 ± 1.2	<0.001
<b>Medication use, No. (%)</b>						
Antihypertensive drugs	344 (49.1)	406 (50.8)	467 (51.3)	393 (48.9)	449 (50.3)	0.844
Glucose-lowering drugs	1 (0.1)	10 (1.3)	22 (2.4)	12 (1.5)	16 (1.8)	0.005
Lipid-lowering drugs	5 (0.7)	4 (0.5)	7 (0.8)	10 (1.2)	10 (1.1)	0.479
Antiplatelet drugs	20 (2.9)	35 (4.4)	36 (4.0)	29 (3.6)	29 (3.2)	0.537

\*Variables are presented as Mean ± SD or n (%)

**Abbreviations:** SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; WBC, white blood cell.

## Supplemental Material

**Table S3. The relationship of white blood cell (WBC) counts with new-onset proteinuria in the enalapril only group.**

WBC counts, 10 <sup>9</sup> /L	Events /N (%)	Crude model	Adjusted model*
		OR (95% CI)	OR (95% CI)
Quintiles			
Q1 (<5.1)	26/800(3.3)	Ref	Ref
Q2 (5.1-<5.9)	32/779(4.1)	1.28(0.75, 2.16)	1.23(0.72, 2.09)
Q3 (5.9-<6.7)	25/803(3.1)	0.96(0.55, 1.67)	0.84(0.48, 1.49)
Q4 (6.7-<7.8)	38/870(4.4)	1.36(0.82, 2.26)	1.20(0.71, 2.01)
Q5 (≥7.8)	39/855(4.6)	1.42(0.86, 2.36)	1.27(0.75, 2.13)
Categories			
Q1 (<5.1)	26/800(3.3)	Ref	Ref
Q2-4 (5.1-<7.8)	95/2452(3.9)	1.20(0.77, 1.87)	1.09(0.69, 1.70)
Q5 (≥7.8)	39/855(4.6)	1.42(0.86, 2.36)	1.27(0.75, 2.13)
Categories			
Q1-4(<7.8)	121/3252(3.7)	Ref	Ref
Q5 (≥7.8)	39/855(4.6)	1.24(0.86, 1.79)	1.18(0.81, 1.74)

\*Adjusted for age, sex, body mass index, smoking status, fasting glucose, total cholesterol, triglycerides, high density lipoprotein cholesterol, estimated glomerular filtration rate, uric acid, folate, total homocysteine, *MTHFR* C677T genotypes, systolic blood pressure (SBP) at baseline, as well as time-averaged SBP during the treatment period.

## Supplemental Material

**Table S4. The relationship of neutrophil counts with new-onset proteinuria in the enalapril only group with further adjustment for lymphocyte counts.**

Neutrophil counts, 10 <sup>9</sup> /L	Events /N (%)	Crude model	Adjusted model*
		OR (95% CI)	OR (95% CI)
Categories			
Q1 (<2.7)	18/700(2.6)	Ref	Ref
Q2-4 (2.7-<4.8)	96/2514(3.8)	1.50(0.90, 2.51)	1.34(0.80, 2.26)
Q5 (≥4.8)	46/893(5.2)	2.06(1.18, 3.58)	1.87(1.05, 3.33)
Categories			
Q1-4 (<4.8)	114/3214(3.5)	Ref	Ref
Q5 (≥4.8)	46/893(5.2)	1.48(1.04, 2.10)	1.47(1.02, 2.11)

\*Adjusted for age, sex, body mass index, smoking status, fasting glucose, total cholesterol, triglycerides, high density lipoprotein cholesterol, estimated glomerular filtration rate, uric acid, folate, total homocysteine, *MTHFR* C677T genotypes, lymphocyte counts, systolic blood pressure (SBP) at baseline, as well as time-averaged SBP during the treatment period.

## Supplemental Material

**Table S5. Concomitant medication usage during the treatment period by quintiles of neutrophil counts in the enalapril only group.**

Medication, No. (%)	Neutrophil counts, 10 <sup>9</sup> /L					<i>P</i> value
	Q1(<2.7)	Q2(2.7-<3.3)	Q3(3.3-<4.0)	Q4(4.0-<4.8)	Q5(≥4.8)	
Anti-hypertension drugs						
Calcium channel blockers	542 (77.4)	666 (83.4)	759 (83.3)	646 (80.3)	720 (80.6)	0.016
Diuretics	413 (59.0)	499 (62.5)	556 (61.0)	487 (60.6)	556 (62.3)	0.642
Glucose-lowering drugs	8 (1.1)	13 (1.6)	15 (1.6)	11 (1.4)	17 (1.9)	0.783
Lipid-lowering drugs	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.2)	0.303
Antiplatelet drugs	1 (0.1)	8 (1.0)	7 (0.8)	8 (1.0)	9 (1.0)	0.279

\*Regular concomitant medication use was defined as 180 or more cumulative days of taking the drug of interest.

## Supplemental Material

**Table S6. The relationship of neutrophil counts with new-onset proteinuria in the enalapril only group with further adjustment for calcium channel blocker usage during the treatment period.**

Neutrophil counts, 10 <sup>9</sup> /L	Events /N (%)	Crude model	Adjusted model*
		OR (95% CI)	OR (95% CI)
Categories			
Q1 (<2.7)	18/700(2.6)	Ref	Ref
Q2-4 (2.7-<4.8)	96/2514(3.8)	1.50(0.90, 2.51)	1.31(0.78, 2.20)
Q5 (≥4.8)	46/893(5.2)	2.06(1.18, 3.58)	1.79(1.02, 3.15)
Categories			
Q1-4 (<4.8)	114/3214(3.5)	Ref	Ref
Q5 (≥4.8)	46/893(5.2)	1.48(1.04, 2.10)	1.43(1.00, 2.06)

\*Adjusted for age, sex, body mass index, smoking status, fasting glucose, total cholesterol, triglycerides, high density lipoprotein cholesterol, estimated glomerular filtration rate, uric acid, folate, total homocysteine, *MTHFR* C677T genotypes, systolic blood pressure (SBP) at baseline, as well as time-averaged SBP and calcium channel blocker usage during the treatment period.



## Supplemental Material

**Table S7. Effect modification of neutrophil counts on efficacy of folic acid in prevention of new-onset proteinuria with further adjustment for lymphocyte counts.**

Neutrophil counts, 10 <sup>9</sup> /L	Enalapril	Enalapril-Folic Acid	Crude model		Adjusted model*	
	Events/ N (%)	Events/ N (%)	OR (95% CI)	<i>P</i> for Interaction	OR (95% CI)	<i>P</i> for Interaction
<4.8	114/3214(3.5)	109/3245(3.4)	0.95(0.72, 1.23)	0.044	0.93(0.71, 1.22)	0.035
≥4.8	46/893(5.2)	24/856(2.8)	0.53(0.32, 0.88)		0.49(0.29, 0.82)	

\*Adjusted for age, sex, body mass index, smoking status, fasting glucose, total cholesterol, triglycerides, high density lipoprotein cholesterol, estimated glomerular filtration rate, uric acid, folate, total homocysteine, *MTHFR* C677T genotypes, lymphocyte counts, systolic blood pressure (SBP) at baseline, as well as time-averaged SBP during the treatment period.

## Supplemental Material

**Table S8. Effect modification of neutrophil counts on efficacy of folic acid in prevention of new-onset proteinuria with further adjustment for calcium channel blocker usage during the treatment period.**

Neutrophil counts, $10^9/L$	Enalapril	Enalapril–Folic Acid	Crude model		Adjusted model*	
	Events/ N (%)	Events/ N (%)	OR (95% CI)	<i>P</i> for Interaction	OR (95% CI)	<i>P</i> for Interaction
<4.8	114/3214(3.5)	109/3245(3.4)	0.95(0.72, 1.23)	0.044	0.93(0.71, 1.22)	0.036
$\geq 4.8$	46/893(5.2)	24/856(2.8)	0.53(0.32, 0.88)		0.49(0.29, 0.83)	

\*Adjusted for age, sex, body mass index, smoking status, fasting glucose, total cholesterol, triglycerides, high density lipoprotein cholesterol, estimated glomerular filtration rate, uric acid, folate, total homocysteine, *MTHFR* C677T genotypes, systolic blood pressure (SBP) at baseline, as well as time-averaged SBP and calcium channel blocker usage during the treatment period.

**Table S9. Effect modification of neutrophil counts on efficacy of folic acid in prevention of new-onset proteinuria with further adjustment for annual rate of eGFR decline during the treatment period.**

Neutrophil counts, $10^9/L$	Enalapril	Enalapril–Folic Acid	Crude model		Adjusted model*	
	Events/ N (%)	Events/ N (%)	OR (95% CI)	P for Interaction	OR (95% CI)	P for Interaction
<4.8	114/3214(3.5)	109/3245(3.4)	0.95(0.72, 1.23)	0.044	0.94(0.71, 1.24)	0.040
$\geq 4.8$	46/893(5.2)	24/856(2.8)	0.53(0.32, 0.88)		0.49(0.29, 0.83)	

\*Adjusted for age, sex, body mass index, smoking status, fasting glucose, total cholesterol, triglycerides, high density lipoprotein cholesterol, estimated glomerular filtration rate (eGFR), uric acid, folate, total homocysteine, *MTHFR* C677T genotypes, systolic blood pressure (SBP) at baseline, as well as time-averaged SBP and annual rate of eGFR decline during the treatment period.

Annual rate of eGFR decline, estimated as  $\left(1 - \sqrt[t]{\frac{\text{eGFR at exit}}{\text{eGFR at baseline}}}\right) \times 100\%$ , t is the time length in years from baseline to the exit visit.